Scientists solve structure of complement C5a receptor

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Scientists at Heptares Therapeutics have published the first high-resolution X-ray crystal structure of the complement C5a receptor (a G protein-coupled receptor, GPCR) binding a small molecule allosteric antagonist.

The findings, published in *Nature* today, reveal the location of a new allosteric binding site outside the transmembrane helical bundle and provide insights to the mechanisms by which small molecules interact with and modulate the receptor. This research further emphasises the potential importance and value of structure-based methods to enable the design of selective and optimised small molecules targeting GPCRs for treating a range of diseases.

The C5a receptor (C5a anaphylatoxin chemotactic receptor 1, also known as CD88) plays a key role in the innate immune response. It is part of the complement system, a crucial component of the host response to infection and tissue damage. Activation of the complement cascade generates anaphylatoxins, including the glycoprotein C5a, which exerts a pro-inflammatory effect via the C5a receptor.

Inhibitors of the complement system are of interest as potential drugs for treating diseases including sepsis, rheumatoid arthritis (RA), Crohn's disease and ischaemia-reperfusion injuries. More recently a role of C5a in neurodegenerative conditions such as Alzheimer's disease has been identified. C5a also plays a role in cancer through actions on tumour cells, angiogenesis and regulation of the immune cells in the tumour

microenvironment. Peptide antagonists based on the C5a ligand have been evaluated in clinical trials in psoriasis and RA, however these peptides exhibited problems with off target activity, production costs, potential immunogenicity and poor oral bioavailability.

Fiona Marshall, chief scientific officer of Heptares and Sosei, said, "Our ability to determine the structures of GPCRs with high definition alongside our other structure-based drug design technologies and expertise provides a unique opportunity to tackle high value but difficult targets. With the C5a receptor, these capabilities and the insights they generate provide opportunities to design novel and selective therapeutics to address areas of clear medical need."

More information: Nathan Robertson et al. Structure of the complement C5a receptor bound to the extra-helical antagonist NDT9513727, *Nature* (2018). DOI: 10.1038/nature25025

Provided by Heptares Therapeutics